Title

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Journal

ASAIO Journal, 68(9)

ISSN

1058-2916

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Publication Date

2022-09-01

DOI

10.1097/mat.0000000000001641

Peer reviewed

Published in final edited form as:

ASAIO J. 2022 September 01; 68(9): 1191–1196. doi:10.1097/MAT.0000000000001641.

Utility of Routine Head Ultrasounds in Infants on Extracorporeal Life Support: When is it Safe to Stop Scanning?

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Abstract

Intracranial hemorrhage (ICH) can be a devastating complication of extracorporeal life support (ECLS); however, studies on the timing of ICH detection by head ultrasound (HUS) are from two decades ago, suggesting ICH is diagnosed by day 5 of ECLS. Given advancements in imaging and critical care, our aim was to evaluate if the timing of ICH diagnosis in infants on ECLS support has changed. Patients <6 months old undergoing ECLS 2011–2020 at a tertiary care children's hospital were included. Primary outcome was timing of ICH diagnosis on HUS. Seventy-four infants underwent ECLS for cardiac (54%) or pulmonary (46%) indications. Venoarterial ECLS was most common (88%). Median ECLS duration was 6 days (range 1–26). Sixteen patients were diagnosed with ICH (21.6%), at a median of 2 days post-cannulation (range 1–4). Nearly all were <4 weeks old at cannulation (93.8%). In conclusion, one-fifth of infants developed ICH diagnosed by HUS while on ECLS, all within the first four days of ECLS, consistent with previous literature. Despite advances in critical care and imaging technology, the temporality of ICH diagnosis in infants on ECLS is unchanged.

Keywords

extracorporeal life support; ECLS; pediatric critical care; intracranial hemorrhage; ultrasonography

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Presentations: This work was presented as a Virtual Poster presentation at the 2020 Annual Extracorporeal Life Support Organization Conference.

Introduction

Extracorporeal life support (ECLS) is a potentially life-saving intervention for children with devastating cardiac or pulmonary diseases or injuries.[1] However, ECLS requires anticoagulation to prevent blood from clotting within the circuit, and thus patients are at risk for hemorrhagic events.[2] Approximately 10–20% of infants on ECLS develop intracranial hemorrhage,[2] a potentially devastating complication which is associated with higher mortality[3] and worse developmental outcomes in survivors.[4] In many centers, serial head ultrasounds (HUS) are obtained on infants while on ECLS to evaluate for the presence of ICH.[5]

There is data from the late 1990s suggesting that this may not be necessary beyond five days on ECLS.[6,7] However, most of the research on this topic is now over 2 decades old, and there have been critical advancements and modifications in the management of patients on ECLS, such as reductions in anticoagulation target levels, with some patients undergoing anticoagulation-free trial periods following cannulation.[8] Furthermore, advances in ultrasound imaging technology and neonatal and pediatric critical care may have altered the prevalence and timing of ICH development and diagnosis in this patient population. It remains unknown if the advances over the past two decades have resulted in earlier detection of ICH in this population. Thus, updated information on the highest risk period for ICH development in this critically ill population is needed. Several studies have investigated risk factors for ICH in infants, identifying patient characteristics such as gestational age,[9] acidosis,[9] and coagulopathy.[10] In particular, thrombocytopenia has been identified as a risk factor for ICH in some populations,[10] but is not associated with ICH in other studies.[11] The ideal platelet count at ECLS initiation and for the duration of ECLS remains unknown.

We hypothesized that, in comparison to the data from the late 1990s and due to advances in imaging technology and neonatal critical care, most ICH would be detected earlier, within the first three days of initiation of ECLS, and that obtaining further head ultrasounds would not change clinical practice. Additionally, we hypothesized that pre-ECLS coagulopathy would be associated with development of ICH.

Materials and Methods

Institutional review board approval was obtained (IRB # 1582549) with a waiver of informed consent. Patients were identified from an institutional prospectively collected ECLS registry. Our institution is a large tertiary care pediatric referral center, with approximately 10–20 pediatric ECLS cannulations per year. ECLS cannulations during this study period were performed by three pediatric cardiothoracic surgeons and ten pediatric general surgeons, all experienced in ECLS cannulation. Patients undergoing ECLS for congenital heart disease were primarily cannulated by the pediatric cardiothoracic surgery attendings, while the pediatric general surgeons performed ECLS cannulation for the other indications listed below. We utilize the Maquet Rotaflow Pump with the Quadrox Oxygenator (Getinge AB). Protocolized transfusion thresholds on ECLS include hematocrit < 30%, platelet count < 100,000, and fibrinogen < 200 mg/dL. If there is no evidence of bleeding by day five of ECLS, the platelet transfusion threshold is lowered to 75,000.

Intravenous heparin is used for anticoagulation, with a target range of activated partial thromboplastin time (aPTT) of 60–80. Starting in 2018, our protocol switched to using anti-Xa levels, targeting a range of 0.3–0.7 international units per ml. Our protocol is to obtain HUS three times a week for the duration of ECLS. When possible, brain MRIs and/or computed tomography scans (CTs) are obtained after the infant has been separated from ECLS to evaluate for pathology.

Inclusion criteria were patients aged younger than 6 months who underwent ECLS cannulation between July 2011 and February 2020. Exclusion criteria was ICH diagnosed prior to ECLS cannulation. Patients with more than one ECLS run had data from the first ECLS run only analyzed. Data were collected on demographics, ECLS indication, ECLS access details, laboratory values, imaging results, ECLS complications, and mortality. The primary outcome was timing between initiation of ECLS and radiographic diagnosis of ICH on head ultrasound (HUS). Secondary outcomes included the overall rate of ICH in the cohort, and risk factors for ICH. Multivariable logistic regression was performed to identify independent risk factors for ICH.

Descriptive statistics were performed for baseline characteristics. Categorical data are presented as proportions and percentages. All continuous data were non-parametric and are presented as median and interquartile range (IQR). Outcomes were compared between patients with and without ICH diagnoses. Patient age was sub-classified as ≤ 28 days old or > 28 days old for further analysis of effect of age on outcomes. Categorical variables were compared using chi-square tests or Fisher's exact test when appropriate. Continuous variables were compared with Mann-Whitney-U tests. Patient factors associated with ICH development on univariate analysis or clinically relevant from literature review were included in a multivariate regression model. The level of significance was set at $p < 0.05$. Analysis was conducted using SAS (SAS, version 9.45; SAS Institute Inc).

Results

Overall Results

Seventy-eight infants underwent ECLS during the study period (Table 1). Four had pre-cannulation head ultrasounds (HUS) showing ICH and were excluded from this study. The 74 infants that met inclusion criteria underwent ECLS cannulation at a median age of 4 days old (IQR 1–46). The majority were male (58.1%). The most common indication for ECLS was congenital heart disease (48.7%), followed by persistent pulmonary hypertension of the newborn (PPHN, 18.9%) and congenital diaphragmatic hernia (CDH, 10.8%). Twenty-four patients (32.4%) were placed on ECLS within 6 hours of cardiac surgery. Cardiopulmonary resuscitation (CPR) was required prior to ECLS cannulation in 27.0% and the vast majority were on vasopressors prior to ECLS (90.5%). Patients were acidotic (median pH 7.22) and hypoxic (median PaO_2 43 mmHg) prior to ECLS. The majority underwent venoarterial ECLS (87.8%), and most were cannulated in the neonatal intensive care unit (NICU, 41.9%) or the pediatric ICU (PICU, 32.4%). ECLS cannulation was performed by pediatric cardiothoracic surgery (58.1%) or pediatric general surgery (41.9%) in all cases. The median duration of ECLS was 6 days (IQR 4–10) and the median hospital length of stay (LOS) was 31.5 days (IQR 15–69.8, range 2–420 days). In-hospital mortality was 44.6% (Table 2).

Head Imaging

Seventy-four patients underwent a total of 318 head ultrasounds while on ECLS. Most patients had pre-ECLS head ultrasounds performed (78.4%). While on ECLS, patients had a median of 3.5 HUS performed (range 1–14). The most common number of HUS performed was 3 (n = 17/74, 23.0%), and these patients were on ECLS for a median of 5 days. Eleven patients had one HUS performed (14.9%), while nine patients had 2 HUS performed (12.2%), all with a median ECLS duration of 3 days. Ten patients had 4 HUS performed (13.5%) and eight patients had 5 HUS performed (10.8%), all with a median ECLS duration of 7.5 days. The remaining nineteen patients (25.7%), had 6 or more HUS performed, and these patients were on ECLS for a median of 14 days.

The majority of these HUS (240/318, 75.5%), did not show evidence of ICH. Sixteen patients (21.6%) were diagnosed with ICH on HUS while on ECLS. The median timing of ICH diagnosis was the second day of ECLS, and no ICH were diagnosed after the fourth day on ECLS (Figure 1). Half of the initial ICH were diagnosed as grade 1, seven were grade 2, and one was grade 4. Seven patients had progression of ICH to a higher grade (43.8%). These were most commonly to grade 4 (n=5/7, 71.4%) with two patients progressing to grade 3 ICH (28.6%). Progression of ICH occurred at a median of two days after initial diagnosis (range 0–8 days) (Figure 2). Patients who developed ICH underwent a median of four HUS while on ECLS (IQR 3–6) compared to a median of 3 HUS (IQR 2–5) in patients who did not develop ICH (p = 0.20). Overall, half of patients who developed an ICH (n=8/16) were decannulated as a result of the ICH, and the vast majority (7/8, 87.5%) subsequently died.

Forty-one patients were on ECLS for longer than four days (median 8 days). All patients on ECLS for longer than four days had at least one additional HUS obtained after day four of ECLS (median 3 additional HUS, range 1–12), accounting for a total of 155 additional HUS, or 3.8 HUS per patient after day four. Nine of these patients were part of the cohort who developed ICH, and these patients had a median of two additional HUS performed after day four of ECLS (range 1–8). Thirty-two patients without ICH who were on ECLS for > 4 days continued to have HUS performed, with a median of 3 HUS (range 1–12), for a total of 126 additional HUS, or 3.9 exams per patient. Thus, 40% (126/318) of the HUS performed while on ECLS were in patients without ICH, and performed after day four of ECLS, when no further ICH were diagnosed.

Ten patients underwent head computed tomography (CT) imaging within 30 days of ECLS decannulation (13.5%), while thirty patients had brain magnetic resonance imaging performed (40.5%). Of the 16 patients who had ICH diagnosed on HUS, six had a head CT performed and two-thirds of these had evidence of ICH on head CT (n = 4/6). Of patients without ICH on HUS, only four had a subsequent head CT, and all of these had no evidence of ICH.

Eight patients with ICH had a subsequent brain MRI within 30 days of ECLS decannulation. The majority (75.0%, n = 6/8) had evidence of ICH on MRI. Of the 58 patients without ICH on HUS, 22 had a subsequent brain MRI, at a median interval of 6 days from ECLS decannulation (IQR 4.25–11.5, range 2–20 days). Seven of these patients had evidence of

ICH on the brain MRI despite a negative HUS, including subdural hematomas (n = 4), epidural hematomas (n = 1), punctate hemorrhage foci (n = 1) and hemorrhagic infarcts (n = 1). Of these seven patients, the median interval between last HUS while on ECLS and subsequent MRI was 7 days (range 4–10 days). Additionally, in four of these patients, the final HUS on ECLS was taken on the day of decannulation, two patients had their final HUS performed 1 day prior to decannulation, and one patient had their last HUS performed 2 days prior to decannulation.

Risk Factors for Development of ICH

Infants who developed ICH on ECLS were of similar gestational ages and birth weights to those who did not develop ICH (37.6 weeks vs 38.6 weeks, p = 0.68; 2.8 kg vs. 3.0 kg, p = 0.73, Table 3). They were slightly younger at time of ECLS cannulation (2 vs. 6 days old, p = 0.07), and weighed slightly less (3.3 kg vs. 3.5 kg, p = 0.06). A lower pre-ECLS platelet count (148,000 vs. 219,000, p = 0.004) and higher INR (1.61 vs. 1.39, p = 0.017) were associated with development of ICH. Patients who developed ICH were more likely to have a pre-ECLS platelet count of < 150,000 (53.3% vs. 20.4%, p = 0.02). Patients who developed ICH had a slightly higher rate of in-hospital mortality (62.5% vs. 39.7%, p = 0.1) (Table 4). Pre-ECLS CPR, ECLS duration, and hospital LOS did not differ between groups. While there was no significant difference in the total number of HUS obtained while on ECLS (median 4 in ICH cohort vs. 3 in no ICH cohort, p = 0.19), patients with ICH had significantly more HUS per days of ECLS (median 1 HUS per day in ICH cohort vs. 0.6 per day in no ICH cohort, p < 0.001).

On multivariable logistic regression, platelet count below 150,000 remained a significant risk factor for ICH when adjusting for gestational age, age ≤ 28 days old at ECLS, weight at cannulation, pre-ECLS elevated INR, pre-ECLS acidosis measured by base deficit, and pre-ECLS CPR, (OR 5.12, 95% CI 1.12–23.31, p = 0.03) (Table 5).

Discussion

In this single center retrospective review of neonatal extracorporeal life support patients, we found that intracranial hemorrhage was diagnosed by head ultrasound in 21.6% of patients, and all patients who were found to have ICH on HUS were diagnosed by the fourth day of ECLS. Based on our findings, we speculate that further routine screening head ultrasounds after the fourth day of ECLS in patients with previously normal imaging on ECLS may not be necessary. These additional HUS exams in patients without ICH by day four of ECLS accounted for 40% of all HUS obtained on ECLS in this study population. Ongoing surveillance imaging may be more strongly considered in patients at heightened risk for ICH. In particular, the vast majority of infants who developed ICH were ≤28 days old at cannulation. Despite the advances in critical care and imaging technology since previous studies published evaluating the timing of ICH diagnosis in this population, we found that the timing of ICH diagnosis is essentially unchanged. Additionally, we identified several risk factors for ICH in our population on univariate analysis, including pre-ECLS coagulopathy. On multivariable regression, pre-ECLS platelet count < 150,000 remained an independent risk factor for the development of ICH.

Early detection of ICH in infants on ECLS is of paramount importance as the development of ICH is associated with increased mortality[3] and poor neurodevelopmental outcomes.[4] In response to complications such as ICH and surgical site bleeding, efforts have been made to reduce the level of anticoagulation required, including the development of heparin-coated centrifugal pump systems allowing delayed initiation of anticoagulation,[12] and electing to delay anticoagulation when possible until chest tube drainage decreases in post-operative congenital cardiac patients.[8] In addition to these steps, frequent neuromonitoring is often performed, with common practice being to obtain daily head ultrasounds in infants on ECLS although the utility of this practice has been questioned. In a study of thirty infants who developed ICH on ECLS from 1996, 85% of all ICH occurred within 72 hours of ECLS initiation.[7] Subsequently, in a 1998 study of fifty-two infants who developed ICH on ECLS, 93% were diagnosed within the first five days of ECLS.[6] Although our 21.6% rate of ICH is similar to the 1998 study (17.5%), we found that all ICH were diagnosed within the first 4 days of ECLS. Thus, despite two decades of advances in critical care and imaging technology, the data on the timing of ICH diagnosis in this population is essentially unchanged. Contrary to our hypothesis, that ICH would be diagnosed earlier, by day 3 of ECLS, due to these advances, it appears that the high-risk period remains through day 4–5 of ECLS. Thus, our data in conjunction with prior work suggest that routine daily head ultrasounds after four days of normal cranial imaging in infants on ECLS may not be necessary.

The Extracorporeal Life Support Organization (ELSO) recommends obtaining a baseline HUS followed by daily HUS for the first 3–5 days on ECLS.[13] Additionally, follow-up MRI is recommended as it is the gold standard for intracranial injury in this population.[13] A recent study of 44 infants who had post-ECLS brain MRIs performed found a sensitivity of only 36% for HUS in detecting intracranial hemorrhage that was subsequently detected on MRI.[14]. These findings underscore the importance of post-ECLS cross sectional imaging, which may aid in both diagnosis of intracranial injury and prognostication.[4]

There are several known risk factors for the development of ICH on ECLS in infants,[15] including gestational age,[9] post-conceptual age,[16] pre-ECLS CPR,[17] acidosis,[9] and coagulopathy.[10] In our study, we identified age ≤ 28 days old at ECLS, lower platelet count and higher INR pre-ECLS as risk factors for ICH on univariate analysis, however only pre-ECLS platelet count of < 150,000 remained significant after adjusting for covariates. The ideal platelet count for infants on ECLS remains unknown and transfusion thresholds vary by institution.[18] Our data suggest that optimizing pre-ECLS coagulopathy may be associated with a lower incidence of ICH on ECLS, but does not answer the important question of ideal platelet counts while on ECLS. Further work is needed to identify ideal transfusion practices in this population.

Our study has several limitations. Although the study setting was a tertiary care center, this is a single center retrospective study, and our results may not be applicable to the broader population. Additionally, our sample size of 74 infants is small, but our primary outcome, timing of ICH development, is not available in larger databases such as ELSO. However, we may have been underpowered to detect differences in secondary outcomes. Our finding that all ICH that were diagnosed by HUS occurred within four days of ECLS

cannulation must be interpreted in the context of our data; the median duration of ECLS was six days, and thus we cannot extrapolate our data to patients with significantly longer ECLS runs. However, 41/74 patients (55.4%) had an ECLS duration longer than four days, and 14/74 (18.9%) were on ECLS for longer than 10 days; thus, we believe that our findings are relevant for the majority of infants on ECLS. Additionally, determining the sensitivity and specificity of HUS in the detection of ICH compared to MRI was not possible due to the low numbers of patients undergoing MRI or CT. Patients may be more likely to undergo an MRI if there is suspicion for neurologic injury, however not all post-ECLS patients undergo MRIs for a variety of reasons, including concerns for the potential risks of anesthesia in a child with a normal or improving neurologic exam. Additionally, patients who died while on ECLS or shortly after decannulation are generally not able to obtain MRIs. Lastly, the additional ICHs detected on MRI may have occurred in the time period between last HUS and MRI and may not have occurred while on ECLS. We may not have accounted for potential confounders affecting the management of the individual patients or the development of ICH, and prospective, multi-institutional studies are needed to guide recommendations on the ideal frequency of screening head ultrasounds in infants on ECLS.

Intracranial hemorrhage is a serious complication of extracorporeal life support. In this single center retrospective study, 21.6% of infants on ECLS developed ICH. All ICH that were detected on HUS while on ECLS were diagnosed within the first four days of ECLS, consistent with studies performed two decades ago, suggesting that advances in critical care and ultrasound imaging technology have not been associated with earlier ICH detection in this population. Additionally, pre-ECLS coagulopathy, particularly platelet count < 150,000, was associated with ICH development. Thus, in infants with normal head ultrasounds for the first four days on ECLS, further routine surveillance head ultrasounds may not be warranted in the absence of neurologic findings.

Conflicts of Interest and Source of Funding:

The authors have no conflicts of interest to declare. The project described was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR001860 for author CMT. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References:

1. Trivedi P, Glass K, Clark JB, et al. Clinical outcomes of neonatal and pediatric extracorporeal life support: A seventeen-year, single institution experience. Artif Organs 43:1085–1091, 2019. [PubMed: 31188477]
2. Dalton HJ, Reeder R, Garcia-Filion P, et al. Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. Am J Respir Crit Care Med 196:762–771, 2017. [PubMed: 28328243]
3. Polito A, Barrett CS, Wypij D, et al. Neurologic complications in neonates supported with extracorporeal membrane oxygenation. An analysis of ELSO registry data. Intensive Care Med 39:1594–1601, 2013. [PubMed: 23749154]
4. Griffin MP, Minifee PK, Landry SH, et al. Neurodevelopmental Outcome in Neonates after Extracorporeal Membrane Oxygenation: Cranial Magnetic Resonance Imaging and Ultrasonography Correlation. J Pediatr Surg 27:33–35, 1992. [PubMed: 1552440]
5. Lin N, Flibotte J, Licht DJ. Neuromonitoring in the neonatal ECMO patient. Seminars in Perinatology 42:111–121, 2018. [PubMed: 29397959]

6. Khan AM, Shabarek FM, Zwischenberger JB, et al. Utility of daily head ultrasonography for infants on extracorporeal membrane oxygenation. J Pediatr Surg 33:1229–1232, 1998. [PubMed: 9721992]
7. Biehl DA, Stewart DL, Forti NH, et al. Timing of Intracranial Hemorrhage During Extracorporeal Life Support. ASAIO J 42:938–41, 1996. [PubMed: 8959265]
8. von Stumm M, Subbotina I, Biermann D, et al. Impact of delayed systemic heparinization on postoperative bleeding and thromboembolism during post-cardiotomy extracorporeal membrane oxygenation in neonates. Perfus (United Kingdom) 35: 626–632, 2020.
9. Hardart GE, Fackler JC. Predictors of intracranial hemorrhage during neonatal extracorporeal membrane oxygenation. J Pediatr 134:156–159, 1999. [PubMed: 9931522]
10. Doymaz S, Zinger M, Sweberg T. Risk factors associated with intracranial hemorrhage in neonates with persistent pulmonary hypertension on ECMO. J Intensive Care 3:4–8, 2015. [PubMed: 25705429]
11. Anton-Martin P, Journeycake J, Modem V, et al. Coagulation profile is not a predictor of acute cerebrovascular events in pediatric extracorporeal membrane oxygenation patients. ASAIO J 63:793–801, 2017. [PubMed: 28678046]
12. McMullan DM, Emmert JA, Permut LC, et al. Minimizing bleeding associated with mechanical circulatory support following pediatric heart surgery. Eur J Cardiothoracic Surg 39:392–397, 2011.
13. Wild KT, Rintoul N, Kattan J, et al. Extracorporeal Life Support Organization (ELSO): Guidelines for Neonatal Respiratory Failure. ASAIO J 463–470, 2020.
14. McCutcheon KC, Wise L, Lewis K, et al. The utility of cranial ultrasound as a screening tool for neonatal ECMO. J Perinat Med 48:173–178, 2020. [PubMed: 31821168]
15. De Mol AC, Liem KD, Van Heijst AFJ. Cerebral aspects of neonatal extracorporeal membrane oxygenation: A review. Neonatology 104:95–103, 2013. [PubMed: 23817232]
16. Hardart GE, Hardart MKM, Arnold JH. Intracranial hemorrhage in premature neonates treated with extracorporeal membrane oxygenation correlates with conceptional age. J Pediatr 145:184–189, 2004. [PubMed: 15289764]
17. Dela Cruz T, Stewart D, Winston J, et al. Risk factors for intracranial hemorrhage in the extracorporeal membrane oxygenation patient. J Perinatol 17:18–23, 1997. [PubMed: 9069059]
18. Cashen K, Meert K, Dalton HJ. Platelet Count and Function during Pediatric Extracorporeal Membrane Oxygenation. Semin Thromb Hemost. 46:357–365, 2020. [PubMed: 32232826]

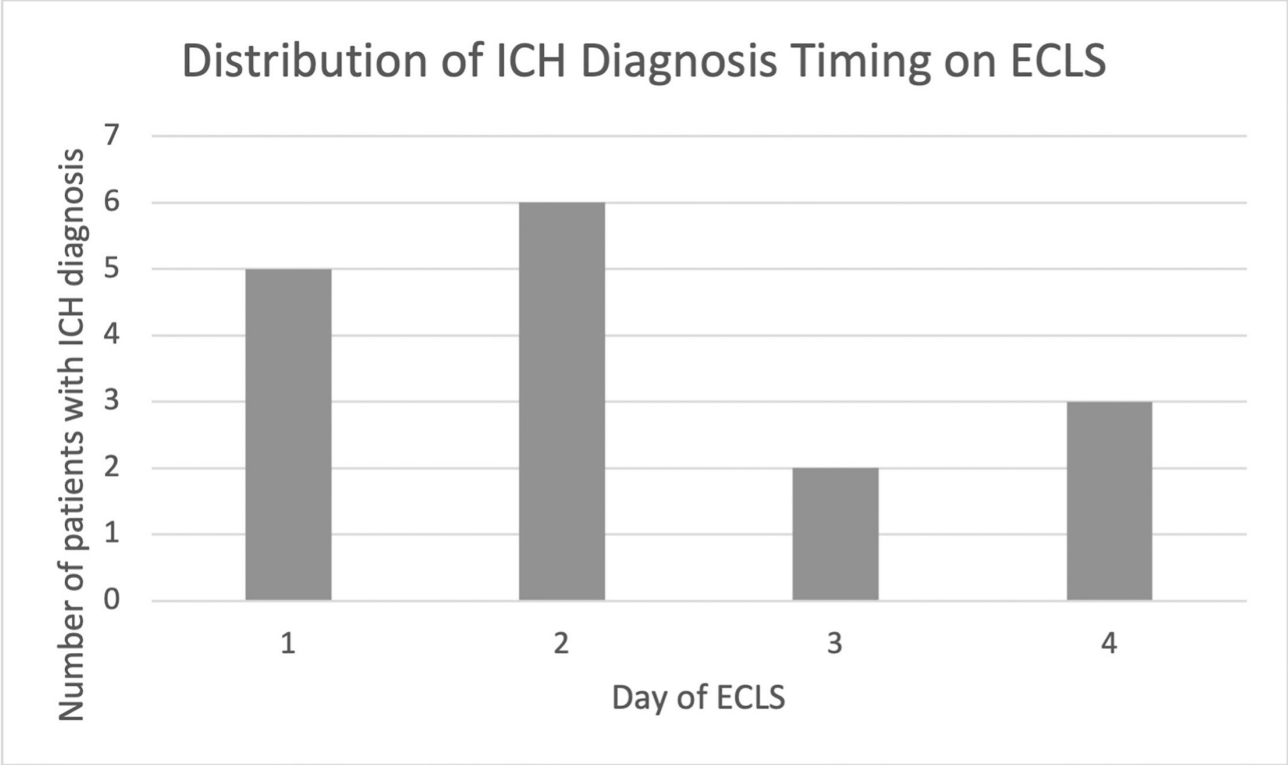

Figure 1: Distribution of Intracranial Hemorrhage Diagnosis Timing on Extracorporeal Life Support.

ICH: intracranial hemorrhage; ECLS: extracorporeal life support.

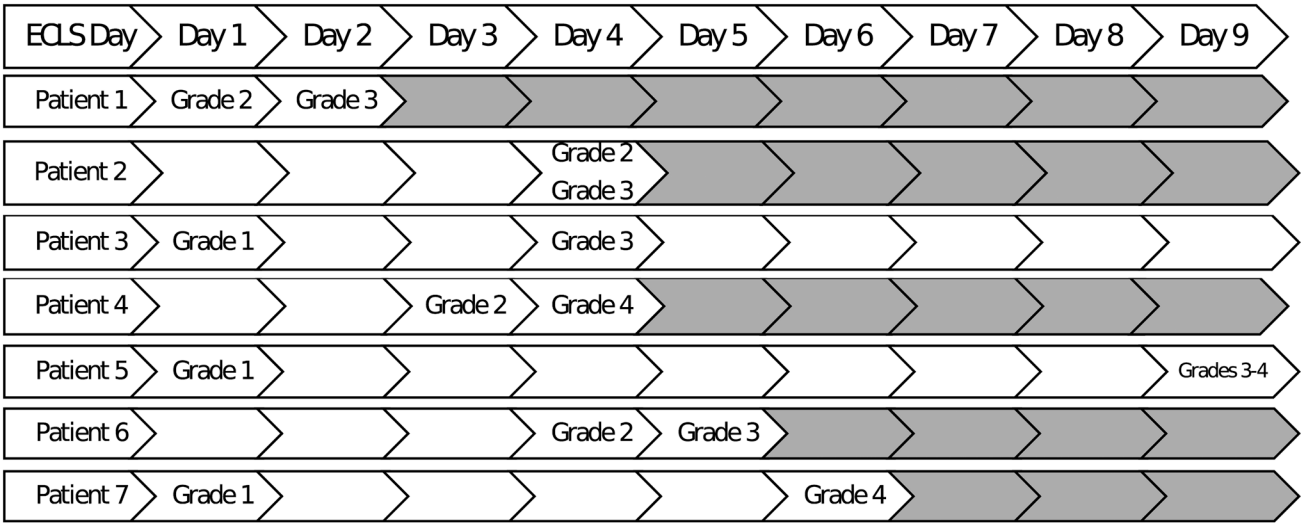

Figure 2: Timing of Initial Intracranial Hemorrhage and Progression to Higher Grade on Extracorporeal Life Support (ECLS).

White boxes indicate days patients were on ECLS; gray boxes indicate that the patient was no longer on ECLS. Note Patient 2 had their initial ICH diagnosed on ECLS day 4 and on the same say it progressed from Grade 2 to Grade 3.

Table 1:
Baseline characteristics of all infants requiring extracorporeal life support.

IQR: interquartile range; kg: kilograms; ECLS: extracorporeal life support; PPHN: persistent pulmonary hypertension of the newborn; CPR: cardiopulmonary resuscitation; PaO_2: arterial partial pressure of oxygen; INR: international normalized ratio; PTT: partial thromboplastin time; NICU: neonatal intensive care unit; PICU: pediatric intensive care unit; OR: operating room; MRI: magnetic resonance imaging.

Variable	All Infants n = 74
Age, days: median (IQR)	4.0 (1–46)
Age ≤ 28 days old: n (%)	54 (73.0)
Gestational age, weeks: median (IQR)	38.4 (36.9–39.4)
Birth weight, kg: median (IQR)	2.9 (2.5–3.5)
Weight at ECLS cannulation, kg: median (IQR)	3.5 (2.9–4.1)
Sex, % female: n (%)	31 (41.9)
ECLS Indication: n (%)	
Congenital heart disease	36 (48.7)
PPHN	14 (18.9)
Congenital diaphragmatic hernia	8 (10.8)
Meconium aspiration	7 (9.5)
Cardiac arrest	4 (5.4)
Viral pneumonia	3 (4.1)
Acute respiratory failure	2 (2.7)
Pre-ECLS CPR: n (%)	20 (27.0)
Pre-ECLS vasopressors: n (%)	67 (90.5)
Pre-ECLS pH: median (IQR)	7.22 (7.09–7.35)
Pre-ECLS base deficit, median (IQR)	−5 (−11 to 0.9)
Pre-ECLS PaO_2, mmHg: median (IQR)	43 (31–59)
Pre-ECLS hemoglobin, g/dL: median (IQR)	13.7 (12.3–15.5)
Pre-ECLS platelet count, $\times 10^3$: median (IQR)	201 (148–274)
Pre-ECLS INR: median (IQR)	1.43 (1.25–1.61)
Pre-ECLS PTT: median (IQR)	53.0 (42.9–70.0)
Pre-ECLS fibrinogen, mg/dL: median (IQR)	177 (151–231)
ECLS type: n (%)	
Venoarterial	65 (87.8)
Venovenous	9 (12.2)
ECLS cannulation location: n (%)	
NICU	31 (41.9)
PICU	24 (32.4)
OR	18 (24.3)
MRI	1 (1.4)

Table 2:
Outcomes of infants on extracorporeal life support.

ECLS: extracorporeal life support; DIC: disseminated intravascular coagulation; LOS: length of stay.

Variable	All Infants n = 74
ECLS duration, days: n (%)	6 (4–10)
ECLS complications: n (%)	
Renal replacement therapy	22 (29.7)
DIC	15 (20.3)
Circuit clot	22 (29.7)
Circuit change	26 (35.1)
Hospital LOS, days: median (IQR)	30.5 (15–69.8)
In-hospital mortality: n (%)	33 (44.6)

Table 3:
Characteristics of infants with intracranial hemorrhage compared to those without.

ICH: intracranial hemorrhage; IQR: interquartile range; kg: kilograms; ECLS: extracorporeal life support; CPR: cardiopulmonary resuscitation; PaO_2: arterial partial pressure of oxygen; INR: international normalized ratio; PTT: partial thromboplastin time; NICU: neonatal intensive care unit; PICU: pediatric intensive care unit; OR: operating room; MRI: magnetic resonance imaging.

Variable	ICH n = 16	No ICH n = 58	p-value
Age, days: median (IQR)	2 (1.5–5)	6 (1–54)	0.07
Age ≤ 28 days old: n (%)	15 (93.8)	39 (67.2)	0.05
Gestational age, weeks: median (IQR)	37.6 (35.4–40.2)	38.6 (37.0–39.4)	0.68
Birth weight, kg: median (IQR)	2.8 (2.4–3.5)	3.0 (2.5–3.5)	0.73
Weight at ECLS cannulation, kg: median (IQR)	3.3 (2.7–3.6)	3.5 (2.9–4.3)	0.06
Sex, % female: n (%)	8 (50.0)	23 (39.7)	0.60
ECLS Indication: n (%)			
Cardiac	9 (56.3)	31 (53.5)	1.0
Pulmonary	7 (43.7)	27 (46.5)	
ECLS within 6 hours of cardiac surgery: n (%)	6 (37.5)	18 (31.0)	0.76
Pre-ECLS CPR: n (%)	6 (37.5)	14 (24.1)	0.34
Pre-ECLS vasopressors: n (%)	16 (100)	51 (87.9)	0.34
Pre-ECLS pH: median (IQR)	7.20 (7.09–7.34)	7.22 (7.09–7.35)	0.89
Pre-ECLS base deficit, median (IQR)	−7 (−12.2 to −4)	−5 (−11 to 1)	0.36
Pre-ECLS PaO_2, mmHg: median (IQR)	48 (30–103)	43 (31–53)	0.67
Pre-ECLS hemoglobin, g/dL: median (IQR)	14.4 (12.8–16.6)	13.7 (12.2–15.1)	0.22
Pre-ECLS platelet count, $\times 10^3$: median (IQR)	148 (106–193)	219 (161–297)	0.004
Pre-ECLS INR: median (IQR)	1.61 (1.4–2.3)	1.39 (1.2–1.5)	0.017
Pre-ECLS PTT: median (IQR)	52.4 (46.5–112.6)	53.2 (40.2–65.4)	0.19
Pre-ECLS fibrinogen, mg/dL: median (IQR)	153 (109–233)	177 (159–231)	0.32
ECLS type: n (%)			0.67
Venoarterial	14 (93.8)	50 (86.2)	
Venovenous	1 (6.2)	8 (13.8)	
ECLS cannulation location: n (%)			0.52
NICU	7 (43.8)	24 (41.4)	
PICU	7 (43.8)	17 (29.3)	
OR	2 (12.5)	16 (27.6)	
MRI	0 (0)	1 (1.7)	

Table 4:
Outcomes of infants with intracranial hemorrhage compared to those without.

ICH: intracranial hemorrhage; ECLS: extracorporeal life support; DIC: disseminated intravascular coagulation; LOS: length of stay; IQR: interquartile range.

Variable	ICH n = 16	No ICH n = 58	p-value
ECLS duration, days: n (%)	6 (4–8.5)	6.5 (3–10)	0.75
ECLS complications: n (%)			
Renal replacement therapy	3 (18.8)	19 (32.8)	0.36
DIC	5 (31.3)	10 (17.2)	0.29
Circuit clot	5 (31.3)	17 (29.3)	1.0
Circuit change	3 (18.8)	23 (39.7)	0.15
Hospital LOS, days: median (IQR)	19.5 (8–92)	33 (18–70)	0.23
On-ECLS mortality: n (%)	2 (12.5)	13 (22.4)	0.50
In-hospital mortality: n (%)	10 (62.5)	23 (39.7)	0.1

Table 5:
Multivariable logistic regression evaluating predictors of intracranial hemorrhage.

CI: confidence interval; ECLS: extracorporeal life support; INR: international normalized ratio; CPR: cardiopulmonary resuscitation.

Variable	Odds Ratio	95% CI	p-value
Gestational age	1.10	0.76–1.59	0.62
Age ≤ 28 days old	1.02	0.07–15.86	0.99
Weight at ECLS	0.70	0.21–2.3	0.56
Pre-ECLS Platelet count < 150,000			0.03
No	reference	reference	
Yes	5.12	1.12–23.31	
Pre-ECLS INR > 1.3			0.14
No	reference	reference	
Yes	3.08	0.60–35.73	
Pre-ECLS base deficit	1.07	0.97–1.18	0.15
Pre-ECLS CPR	3.08	0.69–13.79	0.14